ORIGINAL ARTICLE

Comparative Study of Opioid Free versus Opioid Anaesthesia in Patients Undergoing Laparoscopic Cholecystectomy

Shakya S, Vaidya P, Paudel B

ABSTRACT

Introduction: Opioids have been used as a part of balanced anaesthesia and have known side effects. Opioid Free Analgesia is an emerging technique, based on avoiding intraoperative opioids. **Aims:** To compare the effectiveness of opioid-free versus opioid based anaesthesia. **Methods:** This comparative study involved 100 patients undergoing elective laparoscopic cholecystectomy under general anaesthesia with American Society of Anaesthesiologists I or II physical status. Out of 100 patients, 50 received Fentanyl (Group A) while another 50 (Group B) received Ketamine and Lignocaine. Parameters measured and compared were the gender, age, weight, ASA physical status, hemodynamic stability, postoperative pain intensity (VAS) and opioid requirements, as well as side effects. **Results:** Both groups were comparable with regards to age, gender, weight, American Society of Anaesthesiologists I or II physical status, mean duration of surgery. There was no significant difference between groups hemodynamics at all assessed times (p>0.05) intraoperatively. Visual Analogue Scale pain score in the first 24 hours postoperatively showed that patients in Group A, at all analyzed time points had higher Visual Analogue Scale scores than Group B, but statistically significant difference was confirmed during the first hour (p = 0.001). Seven(14%) in Group A and 5(10%) patients in Group B got intravenous tramadol only once while 5(10%) patients in Group A required twice, which was statistically significant (p=0.05). Intraoperatively, 2 patients (4%) in group A had bradycardia while none in group B, which was statistically insignificant (p=0.153). Postoperatively, nausea was more in group A than Group B i.e. 8% vs 4% (p=0.4). **Conclusion**: Opioid Free anaesthesia has a better benefit over Opioid anaesthesia with regard to postoperative pain score, opioid consumption and its side effects.

***Keywords*:** Fentanyl, Ketamine, Lignocaine, Opioid, Pain, Tramadol

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INTRODUCTION

Opioid Free Anesthesia (OFA) is an emerging technique along with a recent research perspective. It is based on the idea that avoiding intraoperative opioids would have better postoperative outcomes.[1] This technique avoids intraoperative opioids via any route (systemic, neuraxial, or tissue infiltration).[2] In general anaesthesia opioids are still one of the major drugs, since, they are essential in pain treatment both intra- and postoperative period. Although they are very effective for pain but associated with side effects like somnolence, dizziness, constipation, nausea, vomiting, respiratory depression, itching, urinary retention, etc. Other two most important side effects may include hyperalgesia and opioid tolerance. Multimodal pain treatment have shown promising role in avoiding opioid consumption. It involves the use of non-opioid analgesics and sympatholytic drugs.[3] Multimodal analgesic techniques uses acetaminophen, alpha-2 agonists (dexmedetomidine), esmolol, gabapentinoids, lidocaine, magnesium sulfate, ketamine, dexamethasone, nonsteroidal anti-inflammatory drugs, either alone or in combination, have shown to decrease the requirement of opioids perioperatively.[3,4] Intravenous lidocaine suppresses spontaneous impulses originating from injured nerve fibers and proximal dorsal root ganglions and functions by inhibition of Na-channels, NMDA (N-methyl-D-aspartate) and G-protein coupled receptors.[5] Ketamine, antagonist of NMDA receptor, at high dose, produces anaesthesia while at sub-anaesthetic dose, it is a potent analgesic. Low doses (0.5mg/kg) of ketamine have been proposed to prevent opioid tolerance and opioid-induced-hyperalgesia.[6,7] This study was aimed to compare the effect of opioid-free versus opioid based for general anaesthesia in context to hemodynamic stability, postoperative pain intensity (VAS) and opioid requirements, as well as side effects (nausea, vomiting, itching etc).

METHODS

This hospital based prospective, comparative study was carried out in the Department of Anaesthesiology, NGMC, Kohalpur, Nepal from August 2020 to December 2021 after approval from the Institutional Review Committee. A total of 100 patients willing to give written informed consent fitting into the inclusion criteria (age between 18-65 years, all genders, ASA I & II) were included in this study scheduled for elective laparoscopic cholecystectomy surgery under general anaesthesia.

Patients with known allergy to the study drugs, pregnancy, neurologic or cardiovascular disorder, abnormal renal and liver function, chronic pain disorder, benzodiazepines or opioids abusers,patients with diabetes and psychiatric illness, history of alcohol or drug abuse were excluded from the study. Also, if the patients in the study group developed a sympathetic response to pain by increasing blood pressure and heart rate more than 20% from the initial value during surgery, opioids will be given in the intra-operative period, and the patient will be excluded from the study.

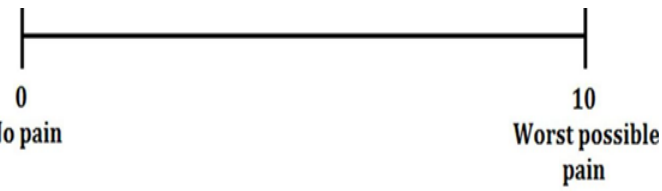
Patients and patient's party were well informed and consent were taken about the anaesthetic procedures and its complications.

These patients were randomly allocated to two groups each consisting of 50 patients by closed envelope technique. Inside the envelope,the group to which the patient belongs was written: Group A: Opioid (fentanyl) Based Anaesthesia (OA) and Group B: Opioid Free Anaesthesia (OFA). Group allocation as well as the study drugs for study to be administered were prepared by the second anaesthesiologist or nurse not involved in the study. The person injecting the study drugs and evaluating the effects were blinded to the drug solution.

Patients from the OA group were induced with fentanyl 1.5mcg/kg, propofol 2mg/kg.

Patients from the OFA group were induced with ketamine 0.5 mg/kg, propofol 2mg/kg along with Lignocaine 1mg/kg.

All the patients admitted to the hospital before surgery underwent complete pre-anaesthetic evaluation including detailed history taking, physical examination and routine pre-operative investigations according to institutional standards. In the preoperative visit the Visual Analogue Scale for Pain (VAS score) was explained to the patient.



Note: A 10 cm baseline is recommended for VAS score.

0: No pain 1-3: Mild Pain 4-6: Moderate Pain

7-9: Severe pain 10: Worst possible pain

All the patients were kept fasting for 6 hours, received and identified in the Operation Theater(OT). An intravenous line was established with an 18G intravenous cannula in a large vein on the dorsum of the left hand or forearm. Demographic data: age, sex, weight, ASA, duration of surgery was recorded and all patients were attached with standard monitors with Heart rate (HR), non-invasive blood pressure (NIBP), respiratory rate (RR), arterial hemoglobin oxygenation by pulse oximeter (SPO2) and electrocardiography (ECG) before the procedure was started and recorded.

Patients in both the study groups were given dexamethasone 0.1mg/kg and 1g paracetamol intravenously (IV) as a preemptive analgesia 1hour before the induction as well ketorolac 0.5mg/kg was given 30 minutes after the intubation. All the patients were administered with glycopyrrolate 0.01mg/kg and midazolam 0.04mg/kg in the OT table before intubation. All patients were preoxygenated with 100% oxygen via face mask for 3 to 5 minutes before induction of anaesthesia. Patient was induced with the allocated group's drug accordingly and orotracheal intubation was facilitated with 0.1 mg/kg vecuronium in all the patients.

All patients were mechanically ventilated with volume-controlled ventilation with a tidal volume of 6-8 ml/kg with 100% oxygen, respiratory rate 16-18 breaths per minute, PEEP 5 cm H_2O. Maintenance of anaesthesia was done with Isoflurane 0.8-1 MAC and vecuronium IV boluses for intraoperative muscle relaxation. Additional fentanyl was administered as needed during anaesthesia with a 20% increase in blood pressure or if the heart rate was greater than 100 beats/min in Group A while if given in group B that subject will be excluded from the study. Laparoscopic port site was infiltrated with 2% Lignocaine 10ml in both the study groups after the closure of the skin. After the completion of surgery, once the patient had return of spontaneous breathing, the residual neuromuscular blockade was antagonized with neostigmine 0.05mg/kg and glycopyrrolate 0.01mg/kg and endotracheal tube was extubated.

Total surgical time (measured in minutes from surgical incision to skin closure) was recorded. On admission to the Post Anaesthetic Care Unit (PACU), a postoperative pain was assessed as soon as the subject was alert and able to answer questions and recorded (first or 0 hour). A level of pain was assessed using a 0 to 10 Verbal Analogue Scale (VAS), and was recorded at 0, 4, 8, 12 and 24 hours (hrs) postoperatively. At the same time, nausea, vomiting, hypertension, hypotension, shivering were assessed and recorded. In PACU, 30 mg of the ketorolac was given 8 hourly for the first 24 hrs to keep the VAS score<7. If the patient was still complaining of pain, 50mg of tramadol IV was given to maintain VAS score≤4. A part from the VAS score, the incidence of PONV was also assessed and if necessary 4 mg of Odansetron IV was given. The total amount of postoperative Tramadol used over 24 hours was recorded.

Statistical Analysis

Data thus recorded and collected were analyzed by standard

statistical tests such as Chi square test and Students unpaired t-test with SPSS version 20. The p value < 0.05 were considered statistically significant.

RESULTS

Both groups were comparable with regards to age, gender, weight, ASA physical status, mean duration of surgery. There was no statistically significant difference between groups (p > 0.05)

Variables	Group A	Group B	p-value
Age(yrs)	37.40 ± 14.05	41.52 ± 11.77	0.359
Gender			
Male	10 (20)	8 (16)	0.271
Female	40 (80)	42 (84)	
Weight (Kg)	53.44 ±7.87	52.98±6.99	0.352
Physical Status			
ASA I	38 (76)	41 (82)	0.461
ASA II	12 (24)	9 (18)	
Duration of Surgery(min)	81.40 ±19.27	76.40±16.26	0.294

Table I: Study population demographic data

There was no significant difference between groups regarding HR, MAP, RR and SpO2 at all assessed times (p > 0.05) intraoperatively (Figure 1, 2 and 3).

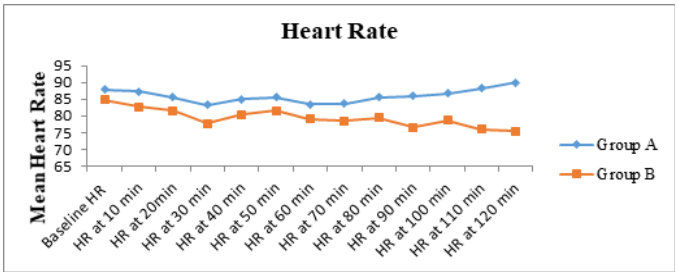


Figure: 1 Mean Heart Rates (beats per min) of the two study groups at different time intervals

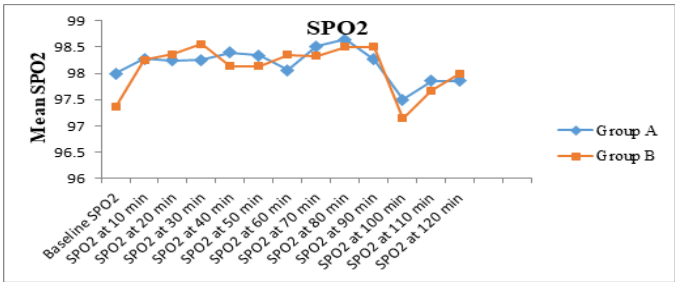


Figure 2: Mean SPO2 of the two study groups at different time intervals

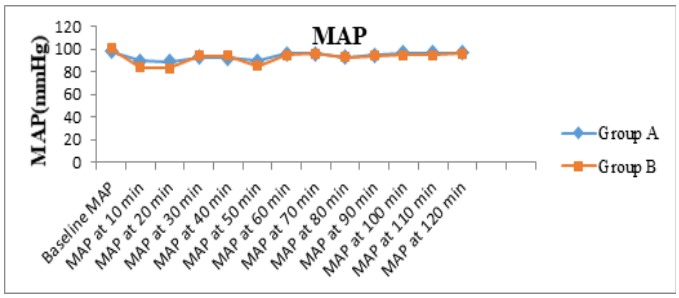


Figure 3: MAP (mmHg) of the two study groups at different time intervals

An analysis of the comparison of the two groups according to VAS pain score in the first 24 hours postoperatively at rest showed that patients in the group A at all analyzed time points had higher VAS scores, compared to patients from the group B, but statistically significant difference was confirmed during the first (0 hour) after the surgery (p = 0.001) (Table II).

Access Time	Group A	Group B	p-value
0 hour	7.74±1.05	5.58±0.64	**0.001**
4 hour	4.10±0.81	4.00±0.83	0.769
8 hour	3.08±0.92	2.92±0.75	0.685
12 hour	2.46±0.65	2.38±0.49	0.084
24 hour	1.78±0.74	1.66±0.69	0.810

Table II: Distribution of the VAS scores at Post operatively during the study

Intraoperatively, 2 patients had bradycardia in group A while none had bradycardia in group B.Bradycardia was treated with IV Atropine 0.6mg and removal of CO_2 gas from the abdomen. Four patients in group A had nausea while 2 patients in group B had nausea postoperatively. No other adverse events were observed in the postoperative period. (Table III)

	Group A	Group B	X^2	p-value
Bradycardia	2 (4%)	0	2.041	0.153
Nausea	4 (8%)	2 (4%)	0.709	0.4

Table III: Comparison between groups with regards to Incidence of Intraoperative Bradycardia and Postoperative Nausea

With regards to total Tramadol consumption in 24 hours postoperatively: 7 patients in group A and 5 patients in group B got IV Tramadol only once,while 5 patients in group A required more than once which was guided by VAS score. Hence, there was a statistically significant decrease in Tramadol consumption in group B (p=0.05). (Table IV)

Tramadol Required in 24 hrs postoperatively	Group A	Group B	X^2	p-value
Not needed	38 (76%)	45 (90%)	5.94	0.05
Once	7 (14%)	5 (10%)		
Twice(100mg)	5 (10%)	0		

Table IV: Comparison between OA and OFA group according to total tramadol consumption 24 h postoperatively (mg)

DISCUSSION

The use of opioid replacement drugs and NSAIDs contributes in reducing treatment costs and promoting patients' recovery.[8] The clinical practice shows that patients with general anaesthesia and high doses of fentanyl - a potent opioid always require higher doses of opioids in the postoperative period that cause Opioid-Induced Hyperalgesia (OIH).[9] Therefore, opioid free anaesthesia (OFA) has been introduced in many countries across the world.

In the present study demographic data in terms of age, gender, weight, ASA physical status, mean duration of surgery were comparable in both the groups. There was no statistically significant difference between the two groups (p>0.05).

This study demonstrated that there were significant difference between the two groups regarding VAS scores at 0 hour postoperatively where it was lower in OFA group than OA group(p=0.001). There was more delay in need for first dose of rescue analgesia in OFA group than OA group. At all analyzed time points had higher VAS scores, compared to patients from the OFA group, but statistically insignificant difference was confirmed during the 4, 8, 12 and 24 hours postoperatively.

Our study results were consonance with the study conducted by Toleska M, Dimitrovski A et al[3] in 2019 who selected 60 patients scheduled for elective laparoscopic cholecystectomy. 30 patients received general anaesthesia with fentanyl 0.002 mg/kg (F group-FG) while other half received opioid-free general anaesthesia (OFA group-OFAG) that included lidocaine 1mg/kg, Ketamine 0.5mg/kg and infusion with lidocaine 2 mg/kg/hr and magnesium sulphate 1.5 g/hr. They concluded that patients in the fentanyl group had higher VAS scores at rest and on coughing in all analyzed time frames 1, 4 , 8, 12 and 24hrs respectively compared to patients from the OFA group, but statistically significant difference was approved 1 and 24hrs (p=0.003 and p=0.002).

Ahmed OH, Noor TME, Ali WM et al[10] in 2020 also reached similar results to our present study. They sampled 62 patients scheduled for laparoscopic cholecystectomy. 31 patients in OA group received fentanyl as the main anesthetic adjuvant and peri-operative analgesics while another 31 in Group OFA received dexmedetomidine, ketamine and paracetamol as an anesthetic adjuvant and peri-operative analgesics. VAS score was higher in the OA group (ranged from 0 – 6) compared to the OFA group (ranged from 0 – 4) but there was no statistically significant difference between both groups regarding postoperative VAS score(p = 0.150).

On the other hand, the study conducted by AlBaharMY, Elbakry AE, Hennawy TA et al[11] in 2022 included 60 patients scheduled for elective laparoscopic cholecystectomy. The OFA group received ketamine (0.25mg/kg), lignocaine (1.5mg/kg) and dexmedetomidine (1mcg/kg over10 min) then 0.5mcg/kg/hr while OA group received fentanyl (1mcg/kg) then 1 mcg/kg/hr as maintenance. There were significant difference in the VAS score as it was lower in OFA group than OA group. This variation may be due to the addition of Dexmedetomidine which we didn't use in our study. It is believed that Dexmedetomidine have analgesic properties.[12] However, this is still on debate and under investigation, the value of adding ketamine to dexmedetomidine has definite merits. Ketamine was proved, at doses less than 0.5mg/kg, to reduce postoperative analgesic needs and this is especially seen in the opioid-tolerant patient.[13] In our study, 14% in OA Group vs 10% in OFA group got single dose of IV Tramadol while 10% patients in OA Group required more than once over 24 hrs postoperatively. Hence, there were statistically significant decrease in Tramadol consumption in OFA group(p=0.05).

Toleska M, Dimitrovski A et al[3] found that the opioids needed in the postoperative period were significantly lesser in the OFA group compared to the opioid group. On the other hand, Ziemann GP, Goldfarb AA, Koppman J[8] et al in 2014 concluded that Opioid-free total intravenous anaesthesia found no difference in opioid consumption post-operative for the same VAS scores but did not explain what the post-operative period was compared.

2 patients in the OA group developed bradycardia (4% vs 0%) during intraoperative. This may be due to peritoneal insufflation with CO_2 gas that led to intraoperative vagal-mediated bradycardia because of sudden peritoneal stretching as patients developed bradycardia during that time.[14] The difference between the incidence of bradycardia was statistically insignificant (p=0.153).

The incidence of PONV (8% vs 4%) were higher in the OA than OFA group. However, the difference between the incidence of PONV was statistically insignificant (p=0.4).No other adverse events were observed in the postoperative period.

Our results were similar to the study conducted by Mansour A, Mahmoud A, Geddawy M[15] et al in 2013 and Soudi AM, Hammad RA, Elshafie MA[16] et al in 2022 respectively which concluded that a decrease in the number of patients who experienced vomiting in the OFA group as compared to OA group but statistically insignificant.

In disagreement with the results of the current study, Mulier JP, Wouters R, Dillemans B[17] et al in 2018 measured the quality of OFA on 50 patients undergoing elective laparoscopic bariatric surgery showed that OFA patients had fewer episodes of PONV along with statistically significance. This may be because all patients received ranitidine 50mg as H_2 receptor antagonist, metoclopramide 10mg other than dexamethasone.

LIMITATIONS

The study has been conducted in laparoscopic cholecystectomy patients only. The current study did not test the sedation status postoperatively,these factor may have affected the outcome and opioids requirements as well.

CONCLUSION

This study clearly showed that the Opioid free Anaesthesia got better benefit over Opioid based Anaesthesia with regards to

post-operative pain score, opioid consumption and side effects.

Conflicts of interest

The authors declare no conflicts of interest.

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